Minor effect of multiple dose omeprazole on the pharmacokinetics of digoxin after a single oral dose

BEREND OOSTERHUIS¹, JAN H. G. JONKMAN¹, TOMMY ANDERSSON³, PETER B. M. ZUIDERWIJK¹ & JAAP N. JEDEMA²

¹Pharma Bio-Research International B.V., P.O. Box 200, NL-9470 AE Zuidlaren, ²Wilhelmina Hospital, NL-9401 KA Assen, The Netherlands and ³AB Hässle, S-431 83 Mölndal, Sweden

- 1 The influence of multiple dose administration of omeprazole on the pharmacokinetics of oral digoxin was studied in 10 healthy male volunteers.
- 2 In a randomized two-way crossover design a single dose of 1 mg digoxin was administered either alone (control) or on day 8 of an 11 day course of omeprazole 20 mg once daily.
- 3 Plasma digoxin concentrations were measured over 96 h after digoxin administration with a [¹²⁵I]-r.i.a. method.
- 4 On average, $C_{\max}$ and AUC values for digoxin were approximately 10% higher and $t_{\max}$ tended to be shorter during the administration of omeprazole, while the elimination rate constant was unaffected.
- 5 The increase in AUC(0,96 h) was statistically significant ($P < 0.05$), but within the accepted range for bioequivalence. In two subjects the increase was approximately 30%.
- 6 It is concluded that co-treatment with omeprazole causes a minor increase in the absorption of oral digoxin. The magnitude of this effect is not considered to be clinically relevant for the majority of patients.

Keywords omeprazole digoxin pharmacokinetic interaction

Introduction

During the clinical development of omeprazole, the potential for interactions was explored with a variety of drugs likely to be given concurrently. These studies have mainly focused on the possible influence of omeprazole on the oxidative metabolism of other drugs. This may be due to the fact that omeprazole has a similar therapeutic indication to cimetidine, which is well-known to influence oxidative drug metabolism. In addition, the structures of both compounds include the imidazole ring, which is considered to be responsible for the inhibition of cytochrome P-450 isoenzymes. Another type of pharmacokinetic interaction can be anticipated from the antisecretory effect of omeprazole and related agents on gastric acid, which could influence gastrointestinal absorption of certain drugs. This latter mechanism could play a role when omeprazole is administered concurrently with digoxin. Digoxin is hydrolysed at low intragastric pH (< 2.5) to its aglycone digoxigenin with the bisdigitoxoside and monodigitoxoside as intermediates, leading to less absorption of intact drug and more absorption of metabolites (Gault *et al.*, 1980, 1981). Thus, cimetidine tends to increase the absorption of digoxin, although the

interaction does not seem to be clinically significant (Somogyi & Muirhead, 1987). The effect of ranitidine on digoxin absorption has not been studied.

We now report a study of the effect of multiple doses of omeprazole on the pharmacokinetics of a single oral dose of digoxin.

Methods

Subjects

Ten healthy non-smoking males, ranging in age from 19–27 years (median 24 years) and ranging in weight from 61–92 kg (median 73 kg) were included in this study. All underwent a complete medical history and physical examination, which included an electrocardiogram, blood count, serum chemistry and urinalysis. The study was approved by the regional Medical Ethics Committee and written informed consent was obtained from each volunteer.

Study design

The study had an open, randomised, two-way crossover design, comprising two periods with administration of a single oral digoxin dose (1 mg) separated by 2 weeks. One of the two doses was administered on day 8 of an 11 day course of oral omeprazole 20 mg daily. Digoxin was given as four immediate release tablets (Lanoxin®; batch no. 87A19), each containing 0.25 mg digoxin. The tablets were swallowed at 10.00 h with 200 ml water. Omeprazole was given once daily as a capsule (batch no. HC8582) containing 20 mg omeprazole as enteric coated granules. Each omeprazole capsule was swallowed at 08.00 h with 200 ml of water before breakfast. No breakfast was taken on digoxin dosing days.

The volunteers were admitted to the Clinical Research Centre of Pharma Bio-Research (9401 PB, Assen, The Netherlands) from the evening before until 72 h after each digoxin administration.

For the administration of the omeprazole doses on days 1–7 and for the 96 h blood sample after digoxin administrations, the volunteers visited an outpatient research unit. Continuous telemetric ECG monitoring was performed for 8 h after digoxin administration and vital signs were determined at regular intervals throughout the study. Venous blood samples (8 ml) for assay of digoxin were collected into heparin-containing polypropylene tubes just prior to, and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72 and 96 h after digoxin administration. Blood samples were centrifuged, and plasma was separated and stored at -20°C until analysis.

Analytical method

The plasma samples were analysed in duplicate for digoxin using the MAGIC [^{125}I]-radioimmunoassay (Corning Medical, Medfield, MA 02052 USA). Daily, three quality control samples containing 0.9, 1.8 and 2.7 (or 2.9) ng ml^{-1} digoxin were also measured in duplicate.

Data analysis

Values of C_{max} and t_{max} were determined by visual inspection of the plasma digoxin concentration-time data.

The terminal elimination rate constant (λ_z) was calculated by log-linear regression, using the last 10 observations on each curve.

AUC values were calculated using the linear trapezoidal rule, with extrapolation to infinity using the value of last measured concentration/ λ_z . Differences in pharmacokinetic parameters between treatments were assessed using two-factor analysis of variance (ANOVA) with subject and treatment as factors. In addition, statistics used to assess bioequivalence were applied. These statistics included the 90% confidence interval of a given parameter during omeprazole treatment, expressed relative to the reference mean (Schuirmans, 1987), and the power of the ANOVA to detect 20% treatment differences at $\alpha = 0.05$.

Results

No serious or severe adverse events were reported during the study. The ECG recordings revealed no pathological changes. In addition, blood pressure, heart rate and oral body temperature did not show marked changes which could have been caused by the study medication.

At each of the digoxin concentration levels of the quality control samples, the assay bias was less than 2% and the coefficient of variation was less than 3%, except for the 0.9 ng ml^{-1} level, where the coefficient of variation was 5.4% ($n = 23$).

In all cases digoxin concentrations in plasma could be measured up to 96 h after dosing. Mean plasma digoxin concentrations, with and without omeprazole, are shown in Figure 1. Table 1 summarizes the values of the pharmacokinetic parameters. On average, C_{max} was

Table 1 Summary of pharmacokinetic parameters of digoxin after a single oral 1 mg dose. OME = administration during omeprazole treatment, CON = control administration

Parameter		Mean	s.d.	Range	90% confidence interval ‡
C_{max} ($\mu\text{g l}^{-1}$)	OME	4.20	1.07	2.62–6.06	85–126
	CON	3.98	0.96	2.58–5.84	
t_{max} (h)	OME	0.75 †		0.50–1.00	
	CON	1.00 †		0.50–1.00	
λ_z (h^{-1})	OME	0.0167	0.0039	0.0106–0.0223	85–111
	CON	0.0170	0.0037	0.0115–0.0235	
AUC(0,96) ($\mu\text{g l}^{-1} \text{ h}$)	OME	55.3	10.5	43.9–70.9	103–119*
	CON	49.7	11.0	34.3–72.0	
AUC ($\mu\text{g l}^{-1} \text{ h}$)	OME	70.1	19.4	51.3–108.4	98–128
	CON	61.9	17.5	37.6–104.3	

* Significant difference between treatments ($P < 0.05$); † median;

‡ 90% confidence interval of mean OME expressed as % of mean CON (from ANOVA).

Figure 1 Plasma concentrations of digoxin during the first 24 h after a single dose of digoxin with (●) and without (○) simultaneous multiple dose treatment with omeprazole (20 mg daily). Mean data of 10 subjects.

Figure 2 Differences in AUC(0,96) of digoxin when administered with and without simultaneous multiple dose treatment with omeprazole (20 mg daily).

slightly higher and $t_{\max}$ tended to be earlier during treatment with omeprazole but these differences were not statistically significant. While λ_z was unaffected, AUC (0,96) increased by approximately 10% during treatment with omeprazole ($P < 0.05$). The changes in AUC (0,96) in individual subjects are shown in Figure 2. Two subjects showed a pronounced (30%) increase. The power of the study to detect a 20% difference at $\alpha = 0.05$ was 0.53 for $C_{\max}$, 0.71 for λ_z , 0.98 for AUC (0,96) and 0.57 for AUC.

Discussion

Plasma digoxin concentrations in the individual subjects showed a similar pattern to those described by others (Ochs *et al.*, 1978, 1980).

The 90% confidence limits on λ_z and AUC(0,96) (Table 1) were confined within the generally accepted

equivalence interval of 80–120%. This was not the case for $C_{\max}$ and AUC. It should be noted, however, that blood sampling was not continued long enough to include 80% of the total area under the plasma curve for most subjects. Combining the above results, it is concluded that concomitant omeprazole treatment increases to a small extent the AUC of orally administered digoxin, probably as a result of increased absorption.

Since most digoxin is excreted in urine either unchanged or as one of the hydrolysis products, the potential for interaction with omeprazole as a result of enzyme inhibition is unlikely. The unchanged elimination rate constant during omeprazole treatment supports this assumption. On the other hand, altered gastric acidity during omeprazole treatment might affect the absorption of orally administered digoxin by decreasing digoxin hydrolysis in the stomach.

Gault *et al.* (1980, 1981) have shown that the intragastric hydrolysis of digoxin is minimal at pH 3, but increases rapidly when the pH falls below pH 2.5. Thus, it is possible that the two subjects with a more pronounced difference in AUC(0,96) between the two treatments had a low intragastric pH when they received the control administration. If this interpretation is correct, then the variability of digoxin AUC should be reduced by omeprazole co-treatment. This is suggested but not proven by the data in Figure 2.

Recently, it has been suggested that the use of an immunoassay might underestimate drug-interactions with digoxin when studied according to the present design (Cohen *et al.*, 1991a,b). The reason would be that immunoassays co-determine the hydrolysis products, namely bis- and monodigitoxoside and digoxigenin. In this respect it is important to take into account the pharmacological activity of these metabolites.

Several estimates of the relative pharmacological activity of digoxin and its hydrolytic metabolites can be found in the literature. Aronson (1977) studied these potencies with respect to inhibition of erythrocyte cation flux (related to membrane Na^+ , K^+ -ATPase activity) and found higher potencies for the mono- and bisdigitoxosides but a lower potency for digoxigenin relative to digoxin. In a cat heart-lung preparation, Böttcher *et al.* (1973) also found considerably higher potency with respect to the effect on contractility for the mono- and bisdigitoxoside as compared with digoxin, whereas digoxigenin was not studied. Lage & Spratt (1966) determined potency ratios from intravenous administration of lethal doses to animals and found similar potencies for digoxin and the mono- and bisdigitoxoside and a considerably lower potency for digoxigenin.

Owing to analytical problems, there is virtually no direct information on relative plasma concentrations of the hydrolytic metabolites and digoxin. From urinary excretion data it can be concluded that the plasma concentration of relatively inactive digoxigenin may be relatively high during the first hours after oral digoxin administration, depending on the acidity of the stomach. However, from 12 h after dosing digoxigenin concentrations are below 4–10% of digoxin concentrations (Gault, 1981). This is consistent with the observation that the hydrolytic metabolites have very short plasma half-lives in comparison with digoxin (Kuhlmann *et al.*, 1974).

Considering the above information, it can be expected

that possible differences in intragastric hydrolysis of digoxin with or without omeprazole would have pharmacological consequences as far as they cause a different systemic availability of digoxin/or the mono- and bisdigitoxoside metabolites. The radioimmunoassay measures all of these compounds at least from 12 to 96 h after digoxin administration which is the most relevant time-interval from a clinical point of view. In this respect it is relevant to note that Cohen *et al.* (1991b), who also studied the omeprazole-digoxin interaction, found an increase in the urinary recovery of unchanged digoxin with omeprazole, as measured by h.p.l.c., which was in the same range (2.5–24.4%) as the increase of AUC observed in our study.

An increase in plasma digoxin concentration by

approximately 30%, as observed in two subjects in this study, could be clinically important. This would be the case for patients already taking digoxin and with serum digoxin concentrations in the upper reaches of the target range when omeprazole was commenced. On the other hand it could be argued that atrophic gastritis among elderly patients, who are likely to form the largest single group receiving digoxin, would lessen the chance and the magnitude of such an interaction.

We conclude that co-treatment with omeprazole causes only a minor increase in the bioavailability of orally administered digoxin. The magnitude of this effect is not considered to be clinically relevant for the majority of patients.

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